Phthalate Exposure and Pulmonary Function

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Exposure to phthalates is widespread because of their use in plastics, cosmetics, and other consumer products. Phthalate exposure has been associated with adverse respiratory outcomes in children. With urinary phthalate measures, we assessed the association between phthalate exposure and four pulmonary function parameters [forced vital capacity (FVC), forced expiratory volume at 1 sec (FEV_1), peak expiratory flow (PEF), and maximum mid-expiratory flow] among the 240 adult Third National Health and Nutrition Examination Survey (NHANES III) participants with urinary phthalate data. Linear regression models controlled for race, age, age squared, standing height, body mass index, cumulative smoking, and current smoking. Monobutyl phthalate (MBP) was significantly associated with decrements in three measures of pulmonary function (FVC, FEV_1, PEF) in males but not in females. For a change from the 25th to the 75th percentile in MBP level among men, FEV_1 decreased 112 mL (SE = 51, $p = 0.03$). Monoethyl phthalate (MEP) was associated with lower FVC and FEV_1 values in men. Monoethylhexyl phthalate (MEHP), the metabolite of the plasticizer commonly used in medical tubing, was not adversely associated with any of the pulmonary function parameters evaluated. Our results suggest that MBP and MEP, but not MEHP, may influence pulmonary function among adult males. *Key words:* monobutyl phthalate, pulmonary function, urine samples. *Environ Health Perspect* 112:571–574 (2004). doi:10.1289/ehp.6564 available via *http://dx.doi.org/* [Online 15 January 2004]

Phthalate exposure is ubiquitous because of use in plastics, cosmetics, and commercial products [Center for the Evaluation of Risks to Human Reproduction (CERHR) 2000a, 2000b, 2000c]. Potential phthalate exposure has been associated with respiratory symptoms and disease in young children through the use of questionnaires to assess surrogates for exposure (e.g., building materials, synthetic bedding; Jaakkola et al. 1999, 2000; Ponsonby et al. 2003). Among Norwegian children, bronchial obstruction was associated with polyvinyl chloride (PVC) building materials in the home (Jaakkola et al. 1999). In Finland, Jaakkola et al. (2000) observed an increased incidence of lower respiratory symptoms among children in homes with plastic wall materials. Australian infants using synthetic bedding materials had higher odds of wheeze at 7 years of age than did other children (Ponsonby et al. 2003). No data on phthalates and respiratory outcomes are available for adults, although beauticians, who are thought to have higher phthalate exposure, have higher rates of respiratory symptoms (Hollund 2001).

Until recently, there was no direct way to measure phthalate exposure in environmentally exposed individuals. A urinary biomarker is now available to assess specific phthalate monoesters (Blount et al. 2000a). This biomarker reflects recent exposure and has been demonstrated to be reliable from one day to the next (Hoppin et al. 2002). To explore the respiratory impact of phthalates in adults, we used urinary levels of phthalate monoesters and linked these to spirometry data collected the same day.

Materials and Methods

We used urinary phthalate data from the 289 participants in the Third National Health and Nutrition Examination Survey (NHANES III) whose urine samples were randomly selected for phthalate analysis (Blount et al. 2000b). Urinary phthalate measures were available only for this small subset of NHANES III participants. Participants in this subgroup were enrolled between 1988 and 1994 and ranged in age from 20 to 60 years. The 240 individuals (140 females, 100 males) with urine samples and complete data on pulmonary function and medical and smoking history were included in this analysis (Table 1). African-American and white subjects were included in this analysis; individuals of other races were excluded because there were few with phthalate measures. Seven phthalate monoesters were measured in spot urine samples using high-pressure liquid chromatography mass spectrometry (Blount et al. 2000b). The four phthalates [monobutyl phthalate (MBP), monobenzyl phthalate (MBzP), monoethyl phthalate (MEP), and monoethylhexyl phthalate (MEHP)] detected in most of the samples were included in this analysis. The remaining three phthalates (monocyclohexyl phthalate, monoisononylphthalate, and mono-octyl-phthalate) were detected in < 25% of the sample and were not included in this analysis.

Pulmonary function measures analyzed were forced vital capacity (FVC), forced expiratory volume at 1 sec (FEV_1), peak expiratory flow (PEF), and maximum mid-expiratory flow (MMEF). We conducted analyses on the FEV_1:FVC ratio as well, but the results were similar to those for FEV_1 and FVC and are not reported here. Spirometry was conducted according to the 1987 American Thoracic Society recommendations [National Center for Health Statistics (NCHS) 2001]. Data were also available on respiratory symptoms, but because of the small sample size and the potential lack of temporal relevance, they were not included in this analysis.

Linear regression analysis was used to evaluate the association between phthalates and pulmonary function parameters. Separate regression models were used for females and males. Regression models were adjusted for age, age squared, standing height, body mass index, cumulative smoking (pack-years), current smoking (cigarettes per day), and race. Smoking was parameterized in several ways. Variables for both cumulative smoking and current smoking were included to adjust for both the long-term effect of smoking on pulmonary function and the positive correlation between cigarettes per day and MBP. Phthalate levels were adjusted for creatinine concentration and log transformed for linear regression analysis. Four individuals (2 men, 2 women) were missing information on MEP, and 18 individuals (3 men, 15 women) were missing information on MEHP. For individuals with missing phthalate information, a value of half the analytical detection limit was assigned for MEP (0.5 ng/mL), and the lowest reported value was used for MEHP (0.04 ng/mL) because this value was lower than half the analytical detection limit (0.6 ng/mL). Regression coefficients were reported for the gender-specific interquartile range for each phthalate.

Results

This subsample of 240 NHANES III participants was similar to the main NHANES III

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population on demographic and smoking status variables with the exceptions of a slightly higher percentage of women (58 vs. 53%) and slightly lower percentage of never smokers (47 vs. 50%; Table 1). The pulmonary function and urinary phthalate values for this subsample are presented in Table 2. MBP levels in urine were significantly associated with decrements in pulmonary function in males but not in females (Table 3). Among males, a change from the 25th percentile to the 75th percentile in MBP concentration was associated with the following changes in pulmonary function: –131 mL (SE = 63, p = 0.04) for FVC, –112 mL (SE = 51, p = 0.04) for FEV_1, and –367 mL/sec (SE = 181, p = 0.05) for PEF. MEP concentration was inversely associated with FVC and FEV_1 among males; these results were no longer statistically significant when the two men with nondetectable levels of phthalates were excluded. When subjects with self-reported asthma and bronchitis were excluded, the associations between MBP and MEP and pulmonary function parameters were virtually unchanged. When we limited analysis to the 37 male never smokers, MBP was significantly associated with decreased FVC with a regression coefficient of –190 (SE = 78, p = 0.02). Other point estimates for nonsmoking men were essentially unchanged from the whole sample. Among the 76 nonsmoking women, MEHP, but not other phthalates, was positively associated with FEV_1 and MMEF. When the analysis was limited to individuals with detectable levels of MEHP, the association between MEHP and FEV_1 was no longer significant. When we ran models using the phthalate levels unadjusted for creatinine concentration, we observed essentially the same results, with the exception that the association between MBP and PEF was no longer statistically significant (p = 0.11).

Discussion

We observed respiratory decrements associated with urinary measures of phthalates in men but not in women. Previous pulmonary function analyses of the NHANES III data identified responses in women, but not in men, associated with serum cotinine measures of environmental tobacco smoke exposure (Eisner 2002). The magnitudes of the associations observed with MBP and MEP among men are similar to those observed for environmental tobacco smoke among women.

Although common in analyses of respiratory health effects, we were unable to limit our analysis to never smokers because of the small sample size. Occupational studies have assessed the effects of respiratory toxicants among all workers without limiting to nonsmokers and have controlled for smoking in their models (Beach et al. 2001; Gardiner et al. 2001; Ulvestad et al. 2000). We adopted this strategy and were able to adjust for both current and lifetime smoking history in our models and to conduct an analysis limited to the small number of never smokers in our sample. The results were essentially the same with the exception of a positive association between MEHP and FEV_1 and MMEF in nonsmoking women. Determining whether this is a chance finding will have to wait until there are larger sample sizes by which to evaluate this question.

Other analyses of respiratory health effects have used surrogates to assess phthalate exposure. Ponsonby et al. (2003) used information on synthetic bedding materials as an indicator of potential phthalate exposure. In studies by Jaakkola et al. (1999, 2000) in Norway and Finland, the questionnaire data on amount of plastic in the home was used as a surrogate for phthalate exposure; the authors assumed that this phthalate was mainly diethylhexyl phthalate (DEHP). Work by Oie et al. (1997) in Norway suggests that even though DEHP has a low vapor pressure, it is commonly found in indoor air on suspended particulate in homes and thus represents a potential route of respiratory exposure. In Boston, phthalates have been detected in the dust and air in a small study of residential and office settings, with high-molecular-weight phthalates (e.g., DEHP) found in higher concentration in

Table 1. Characteristics of the 240 NHANES III participants with urinary phthalate data, 1988–1994, compared with the NHANES III cohort.

	Participants with phthalate data (%)		NHANES participants 20–60 years of age (%)	
Characteristic	Males (n = 100)	Females (n = 140)	Males (n = 5,719)	Females (n = 6,501)
Race				
Black	32	34	31	34
White	68	66	65	63
Smoking history				
Never	37	54	39	60
Current	46	29	37	26
Past	17	17	24	15
Medical history				
Asthma	3	6	6	7
Bronchitis	1	7	3	6
Age at interview (years)				
20–29	24	32	31	30
30–39	28	22	28	30
40–49	31	29	22	22
50–60	17	17	19	18
Body mass index (kg/m^2)				
< 25	39	36	41	41
25–30	31	27	39	29
> 30	30	37	20	30

Table 2. Pulmonary function data and urinary phthalate values for the 240 NHANES III participants with urinary phthalate data, 1988–1994.

	Males (n = 100)			Females (n = 140)		
Measured values	Mean ± SD	Minimum	Maximum	Mean ± SD	Minimum	Maximum
Pulmonary function measures						
FVC (mL)	4,808 ± 808	2,430	7,082	3,472 ± 676	1,527	5,314
FEV_1 (mL)	3,797 ± 678	2,179	5,353	2,822 ± 617	1,144	4,385
PEF (mL/sec)	9,143 ± 1693	4,564	13,210	6,702 ± 1,402	2,584	9,946
MMEF (mL/sec)	3,628 ± 1330	615	6,957	2,969 ± 1,147	419	6,185
Phthalate measures (ng phthalate/g creatinine)[a]						
MBP	30 (2.5)	1.6	962	45 (3.1)	4.7	2,763
MBzP	17 (2.5)	2.1	544	23 (2.4)	2.3	189
MEP	240 (5.4)	0.2	6,786	321 (4.2)	0.5	4,539
MEHP	2 (3.2)	0.05	49	2 (5.0)	0.02	192
Phthalate measures (unadjusted for creatinine, ng phthalate/mL urine)						
MBP	40 ± 2.9	2.2	1,121	43 ± 3.9	4.0	4,665
MBzP	22 ± 3.0	1.84	1,015	22 ± 2.9	1.7	338
MEP	323 ± 6.4	0.50	16,150	307 ± 4.9	0.5	11,192
MEHP	3.3 ± 3.8	0.04	67	2.0 ± 5.8	0.04	66

[a]Geometric means and geometric standard deviations reported for phthalate measures.

dust and low-molecular-weight phthalates (e.g., dibutyl phthalate) found in higher concentrations in air (Rudel et al. 2001, 2003). Although these data indicate that phthalates are found in indoor environments, whether these are associated with plastic materials in the home has not yet been determined.

Hairdressers have higher rates of respiratory symptoms (Hollund 2001; Iwatsubo et al. 2003) and are likely to have higher phthalate exposures due to use of dibutyl phthalates and diethyl phthalates in cosmetics and fragrances. In a recent study, Iwatsubo et al. (2003) reported that hairdressing apprentices had greater reduction in FVC, FEV_1, and MMEF over time compared with office apprentices. Although the hairdressers were predominantly female (85%), the pulmonary function results were similar to those observed among the men in our study for MBP and MEP. Until phthalate measurements are collected among hairdressers and beauticians, we will be unable to evaluate whether MBP and MEP contribute to the observed respiratory health effects among hairdressers.

Of current concern are individuals who are receiving pulmonary therapies through PVC tubing that may contain DEHP, the phthalate most commonly found in medical tubing (Latini and Avery 1999; Tickner et al. 2001). We did not observe an adverse association between MEHP and any of the pulmonary function parameters evaluated.

Identifying sources of phthalates that contribute to urinary levels in the general population is an ongoing research effort. Until recently there were no population data on urinary phthalate levels, and to date there are no published data that indicate sources of exposure associated with biomarkers. Women have been reported to have higher urinary levels than men [Blount et al. 2000b; Centers for Disease Control and Prevention (CDC) 2003], and socioeconomic status and education appear to be weakly associated with phthalate levels (Koo et al. 2002). In this analysis, we observed a positive association between current smoking and MBP levels and thus controlled for this in our models. Whether smoking is directly related to phthalate exposure is not known. The urinary phthalate levels from the NHANES III sample collected from 1988 through 1994 are generally higher than the levels measured in the recent NHANES 1999–2000 (CDC 2003). This may suggest that phthalate levels are decreasing in the U.S. population, although the concentrations are still at measurable levels and the distribution continues to span three orders of magnitude.

We used a biologic measure to assess phthalate exposure. Urinary phthalate measures have a short biologic half-life but are reproducible from one day to the next (Hoppin et al. 2002); long-term reproducibility has not been evaluated. Pulmonary function tests generally represent long-term changes in lung function, although work shift changes in FEV_1 and other pulmonary function tests have been demonstrated (Wang et al. 2003). Whether our measure of phthalates was indicative of long-term exposure, and thus long-term change in pulmonary function, or indicative only of recent exposure, and thus short-term changes in pulmonary function, we cannot determine from our cross-sectional analysis.

Because biologic markers integrate over all exposure routes, we cannot know whether the observed differences in males and females represent different underlying biology or different patterns of exposure. Women have higher levels of MBP on average (Blount et al. 2000b; CDC 2003); however, women may have greater exposure via the dermal route whereas men may have greater exposure via inhalation. Currently, there are no measurement data available to explore the impact of phthalate exposure route on urinary phthalate levels or health outcomes. Previous work assessing phthalate exposure and respiratory function in children relied on surveys of plastic materials in the home (Jaakkola et al. 1999, 2000) and use of synthetic bedding (Ponsonby et al. 2003). These measures may be more likely to capture inhalation exposure via respiratory routes (e.g., off-gassing from phthalate containing materials and suspended particulates) than exposure via dermal routes (Oie et al. 1997). Although our sample may be underpowered to assess the role of all phthalates on pulmonary function, these exploratory results suggest that MBP and MEP may be associated with adverse pulmonary function among adult men.

Table 3. Regression of pulmonary function tests on urinary phthalate levels: 240 NHANES III participants with urinary phthalate data, 1988–1994.

	All participants				Nonsmokers			
	Males (n = 100)		Females (n = 140)		Males (n = 37)		Females (n = 76)	
	β[a]	SE	β[a]	SE	β[a]	SE	β[a]	SE
FVC								
MBP	–131	63*	34	45	–190	78*	76	60
MBzP	–74	68	64	63	–131	102	25	88
MEHP	–75	58	28	42	–42	99	82	71
MEP	–121	58*	37	50	–56	111	21	81
FEV_1								
MBP	–112	51*	42	39	–82	72	73	50
MBzP	–52	56	34	54	–66	89	1	73
MEHP	–45	47	54	36	18	85	134	57*
MEP	–102	47*	67	43	–102	94	36	67
PEF								
MBP	–367	181*	–68	111	–219	224	–6	149
MBzP	–226	196	–153	155	–103	278	–190	216
MEHP	–140	167	83	103	–55	263	215	174
MEP	–250	167	86	124	–240	294	100	198
MMEF								
MBP	–139	127	72	85	219	181	96	106
MBzP	–76	136	–61	120	80	226	–133	154
MEHP	12	116	110	79	267	208	293	120*
MEP	–106	116	162	95	–275	236	132	141

[a]Regression coefficients scaled to the interquartile range (25th–75th percentile) for each phthalate as follows: For men: MBP, 31.53 ng/g creatinine; MBzP, 19.77 ng/g creatinine; MEHP, 3.39 ng/g creatinine; MEP, 608.8 ng/g creatinine. For women: MBP, 54.12 ng/g creatinine; MBzP, 31.15 ng/g creatinine; MEHP, 4.15 ng/g creatinine; MEP, 598.9 ng/g creatinine. Regression models included log creatinine-adjusted phthalate level, race, age, age squared, standing height, body mass index, cumulative smoking, and current smoking. *$p < 0.05$.

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